Scripps Research Study Topples the One Drug-One Disease Paradigm for Combating Protein-Folding Diseases

Findings May Lead To A Novel Therapeutic For Multiple Diseases

LA JOLLA , CA, September 9, 2008—Scientists at The Scripps Research Institute have discovered that a single small molecule may be effective in treating multiple protein-folding diseases, breaking the one drug-one disease approach that has guided the pharmaceutical and biotechnological industries for so many years.

In the new paper, the scientists describe how they were able to restore folding, trafficking, and function to mutant enzymes within cells from patients with two well-known lysosomal storage diseases, specifically Tay-Sachs and Gaucher disease. The scientists accomplished this feat by focusing on the protein maintenance machinery of the cell, enhancing it to fold these mutated enzymes that would otherwise have misfolded and been degraded leading to so-called loss-of-function diseases.

The study was published in the September 5, 2008 edition (Volume 134, Issue 5) of the journal *Cell.*

"Our study demonstrates a new concept that we believe will have broad applicability because it enhances the innate biology of cells to fold mutant proteins and restore their function," said Jeffery Kelly, who is Lita Annenberg Hazen Professor of Chemistry and a member of The Skaggs Institute of Chemical Biology at Scripps Research. We have discovered a single molecule that controls a signaling pathway that regulates protein maintenance machinery, which in turn enables the cell to fold unrelated mutant proteins associated with unique disease such as Gaucher, Tay-Sachs, and cystic fibrosis."

Lysosomal storage diseases such as Gaucher and Tay-Sachs result from a specific inherited deficient enzyme activity that leads to an accumulation of the enzyme's substrate in the lysosomes, organelles in the cell that normally break down these molecules. As a result of lysosomal enzyme dysfunction, cells can be severely damaged, which can lead to serious health problems. There are more than 40 known lysosomal storage diseases, each having a relatively small number of patients. However this new therapeutic strategy allows lysosomal storage diseases associated with misfolding-prone enzymes to be treated as a class, offering the promise of treating numerous diseases with one small molecule, changing the economics of orphan misfolding disease intervention.

In Gaucher disease, patients may bruise easily due to low blood platelets, and may have enlargement of the liver and spleen. Sometimes patients experience fatigue due to anemia. The disease also causes cells in the bone marrow to become engorged with the enzyme's substrate,

which may lead to bone lesions, weakening the skeleton, and sometimes resulting in painful fractures. In some instances, the disease also impairs the function of the lungs.

In Tay-Sachs, a fatal and untreatable lysosomal storage disease common among certain ethnic groups, children who are born with the condition appear to grow normally for the first six months, then suffer from an unstoppable deterioration of mental and physical abilities; death usually occurs before the fourth or fifth birthday.

Protein Folding Restored

To restore enzyme function in cell cultures from patients with Tay-Sachs and Gaucher disease, the scientists used so-called proteostasis regulators--small molecules that regulate the folding capacity of a specific sub-cellular compartment called the endoplasmic reticulum. The scientists showed that two proteostasis regulators, celastrol and MG-132, each individually significantly increased the activity of the mutant misfolding-prone enzymes known to cause the aforementioned maladies.

"One can think of these results as two examples of the same idea," said Kelly. "These two small molecules activate a signaling pathway called the unfolded protein response or UPR that sends a signal to the cell nucleus and results in the coordinated upregulation of numerous protein folding assistants. That upregulation increases the capacity of the endoplasmic reticulum to fold mutant proteins that would otherwise misfold and be degraded. In other words, we have discovered two examples of small molecules that control information going into the nucleus, which can then fix less-than-perfect proteins and make them functional."

While both celastrol, a natural plant product, and MG-132, a proteosome inhibitor, may be too toxic to develop as drugs themselves, they demonstrate proof of principle.

Furthermore, the scientists also showed that the co-application of pharmacologic chaperone and a proteostasis regulator afforded a synergistic rescue of lysosomal enzyme function in patient-derived Gaucher and Tay-Sachs cells. Pharmacologic chaperones are small molecules that bind to a specific mutant enzyme stabilizing it, allowing more of it to properly fold and function.

The scientists achieved a two-fold enzyme function rescue with the proteostasis regulators alone, and roughly the same increase in folding capacity with a pharmacologic chaperone alone. However, when the team applied both types of compounds together, enzyme folding and function rescue increased significantly--to somewhere in the range of a 5 to10 fold increase.

"These findings strongly suggest that this is how diseases like Tay-Sachs will be treated in the future," Kelly said. "Pharmacologic chaperones will be studied and developed independently and so

will proteostasis regulators. There will then be additional studies to demonstrate their synergistic efficacy." These findings also point to the potential of taking a similar approach to ameliorate other loss-of-function diseases, such as cystic fibrosis.

In addition to Kelly, other lead authors of the study, "Chemical and Biological Approaches Synergize to Ameliorate Protein-Folding Diseases," are Laura Segatori (currently an assistant professor at Rice University), Ting-Wei Mu, and Derrick Sek Tong Ong of The Scripps Research Institute and The Skaggs Institute for Chemical Biology. Additional authors include Ya-Juan Wang, William E. Balch, and John R. Yates of Scripps Research.

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